Remarks

Claims 1-24 have been rejected.

Claims 25-30 are withdrawn from consideration as being drawn to non-elected subject matter.

Claims 1-7, 12-14, and 19-24 are canceled by the present amendments.

Claims 8 and 15-18 are amended by the present amendment. The chief amendment is that the limitations of dependent Claims 13 and 14 have been incorporated into independent Claim 8 to better distinguish the invention over cited art. Resultantly, Claims 13 and 14 have been canceled. Also, Claim 8 has been further amended to further define the step of determining the degree of methylation consistent with the application disclosure found, e.g., at page 12, lines 21-23, of the specification. The remaining claim amendments either change claim dependency or address rejections under §112. It is submitted that no new matter has been introduced by amendment of Claims 8 and 15-18.

Claims 8-11 and 15-18 are presented for reconsideration in view of the amendments presented herein and further in view of the following remarks.

Amendments to the Specification

Priority (Item 2 of the Office Action)

The Office Action set forth a requirement that a reference to the prior US priority application US 60/370,690, filed April 9, 2002, to be inserted as the first sentence(s) of the specification or in an application data sheet. The Action further states the conditions for making a timely reference to a prior application depending on the type of prior benefit

claimed and the type of application seeking to rely on the filing date of the prior application, e.g., a utility application entering the national stage from an international application filed on or after November 29, 2000, under 35 U.S.C. 371. The timeliness requirement for such a national stage application is that, after compliance with 35 U.S.C. 371, the specific reference must be submitted during the pendency of the application and within the later of four months from the date on which the national stage commenced under 35 U.S.C. 371(b) or (f) or sixteen months from the filing date of the prior application. See 37 CFR 1.78(a)(2)(ii) and (a)(5)(ii). The time period is not extendable and failure to submit the reference… within the time period is considered a waiver of any benefit of such prior applications… . A benefit claim filed after the required time period may be accepted if it is accompanied by a grantable petition, a surcharge under 37 CFR 1.17(t), and a statement that the entire delay between the date the claim was due under 37 CFR 1.78(a)(2) or (a)(5) and the date the claim was filed was unintentional (paraphrase of Office Action, pages 2-3.)

The Action further clarifies that "If the reference to the prior application was previously submitted within the period set forth in 37 CFR 1.78(a), but not in the first sentence(s) of the specification or an application data sheet (ADS) as required by 37 CFR 1.78(a) (**e.g., if the reference was submitted in an oath or declaration or in the application transmittal letter**)[emphasis added], and the information concerning the benefit claim was recognized by the Office as shown by its inclusion on the first filing receipt, the petition under 37 CFR 1.78(a) and the surcharge under 37 CFR 1.17(t) are not required. Applicant is still required to submit the reference in compliance with 37 CFR

1.78(a) by filing an amendment to the first sentence(s) of the specification or an ADS. MPEP §202.11." (Office Action, pages 3-4.)

In response, the present application is a national stage application filed under 35 U.S.C. 371, having October 8, 2004 as its filing date and the date on which all of the requirements of 35 U.S.C. 371 were met. While the reference to the priority application was not submitted in the first sentence(s) of the specification or in an ADS at the time of filing of the 371 application, a reference to the priority date claimed was included on Applicant's Transmittal Letter CO/EO/US Concerning Submission under 35 U.S.C. 371, next to the international filing date information. That application transmittal letter is date-stamped October 8, 2004 as being received in the PCT division of the USPTO. The USPTO filing receipt for the subject application, dated January 18, 2006, does recognize the priority claim by inclusion of the filing date, April 9, 2002, of the prior US provisional priority application SN 60/370,690. Accordingly, it is submitted that neither petition nor surcharge are required. Applicant has amended herein the first sentence(s) of the specification to include the required reference to the prior application.

Amendment of Brief Description of Drawings

The Brief Description of Drawings which appears at page 4 of the specification has been amended to include an unintentionally omitted brief description of Figure 3. A fuller description of Figure 3 appears on page 12 of the specification, as originally filed. No new matter has been introduced.

All Other Amendments to the Specification

The other amendments to the specification are presented either in response to the Office requirement regarding the use of trademarks in patent applications (see, item 5 of the Office Action) or to correct instances of improper idiom, grammar, and typographical errors. It is submitted that none of these amendments introduces new matter into the application.

Information Disclosure Statement

The Examiner has noted a listing of references throughout the specification does not constitute a proper information disclosure statement, and cited MPEP §609.04(a). (Item 3 of the Office Action.)

In response, Applicant has filed concurrently herewith an Information Disclosure Statement under 37 CFR 1.97(c)(2), listing the documents that are referenced throughout the specification, and supplied copies thereof where required, in order that they may be officially considered.

Oath/Declaration

The oath or declaration filed on October 8, 2004 was deemed to be defective as it was lacking a date of signature by the inventor. (Office Action, item 4.)

In response, Applicant is filing concurrent with this paper a supplemental declaration that is fully executed.

Additionally, Applicant has taken the opportunity to correct a typographical error in the foreign filing date information of the parent PCT application. Namely, the month and

the day of filing were transposed in the original declaration, and hence the European format was inadvertently used. The correct foreign filing date is "04/09/03" for the German PCT application PCT/IB 03/01791.

Lastly, since i) the PTO filing receipt for the subject application has already acknowledged Applicant's priority claim to US provisional application 60/370,690, filed on April 9, 2002, ii) the reference to said prior application was timely made on the application DO/EO/US Transmittal Letter Concerning a Submission under 35 U.S.C. 371 received on October 8, 2004, and iii) a proper amendment referencing the prior provisional application is presently made herein to the first sentence(s) of the specification, Applicant has, for the sake of completeness, taken this opportunity to include the US provisional application number and its filing date information on the supplemental declaration.

Specification – Trademark Usage

Item 5 of the Office Action has noted the use of trademarks in the application and specifically noting that while trademarks have been identified with trademark notations, they must also be capitalized.

In response, Applicant has capitalized the trademark usages and has updated the trademark status of the marks referenced in the application, namely, by amending the trademark notations to reflect a registered mark "®" as opposed to a mark with a pending application for registration "TM". Applicant has also deleted an improper trademark notation on the MethyLight methylation assay. The USPTO trademark database has been searched and there is no pending or registered trademark information on the term

"MethyLight". Lastly, Applicant has inserted the proper notation of a registered trademark for the designated model "ABI PRIZM® 7700", a sequence detector, in the Examples.

Claim Objections

Claim 1 was objected to because the phrase "to be analyzed" in line 1 is redundant to the previous phrase "for analyzing" also in line 1. (Office Action, item 6.)

The objection is rendered moot by the cancellation of Claim 1.

Claim Rejections- 35 U.S.C. §112

Claims 1-7 and 18 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. (Items 7-11 of the Office Action.)

Claims 12 and 24 also appear to be rejected under the same section of the statute, although they were not included in the statement of the rejection (see, Items 12 and13 of the Office Action.)

For the sake of brevity, the rejection as it pertains to Claims 1-7, 12, and 24 will not be restated. Moreover, in an effort to advance the prosecution of the subject application, and without conceding the propriety of the rejection, the rejections of Claims 1-7, 12 and 24 are rendered moot by their cancellation.

Claim 18 has been rejected as being indefinite for use of the phrase "similar to peptides." For the sake of advancing the prosecution and to recite the embodiment of Claim 18 more clearly, Claim 18 has been amended herein. In particular, more specific

language has been taken from the supporting disclosure found at page 11, line 10 et seq., of the specification and inserted in place of the phrase "similar to peptides."

The bases for rejection are believed to be either overcome or removed, and withdrawal of the rejection is respectfully requested.

The Art Rejections

The Rejection of the Claims Under 35 U.S.C. §102(b) or §102(e) as Being Anticipated by Eads et al.

Claims 1-5, 7-10, 12-17, 19-22, and 24 have been rejected under 35 U.S.C. §102(b) as being anticipated by Eads et al (2000.) (Office Action, item 15).

Withdrawal of the rejection as it pertains to Claims 1-5, 7, 12-14, 19-22, and 24 is requested as a result of the cancellation of these claims.

Applicant respectfully traverses the rejection under §102(b) over Eads et al (2000) over the remaining claims, Claims 8-11, and 15-18 amended herein, and requests reconsideration in view thereof and in view of the following distinguishing remarks. The limitations of original dependent Claims 13 and 14 have been incorporated into independent Claim 8 to better distinguish the invention over Eads et al. Resultantly, Claims 13 and 14 have been canceled.

The preferred embodiment recited in Claim 8, amended, requires, in part, [step b] amplifying one or more nucleic acids of the treated nucleic acid in a polymerase enzyme reaction *by means of at least three primer oligonucleotide pairs, wherein one primer pair does not contain a CpG dinucleotide and does not contain a TpG dinucleotide and*

amplifies a reference sequence and the other primer pairs are methylation specific primers, and further wherein the amplificates formed from each species of primer pairs differ respectively in at least one of length, sequence, and a detectable label selected from the group consisting of fluorescence labels, mass labels, and radioactive labels. Further, and now more specifically recited in Claim 8 is the step [step d] of determining the degree of methylation at each analyzed CpG position *from ratios of amplificates formed from each of said methylation specific primers relative to amplificates formed from said primer pair that amplifies said reference sequence.*

The statement of the §102(b) rejection over Eads et al as it pertains to the prior version of Claim 8 is set forth at Office Action, pages 9-10. For the sake of brevity the rejection as it pertains to Claim 8 will not be restated herein, in part because it is believed to be moot as the result of the present claim amendments. Rather, Applicant focuses on the error in the rejection as applied to dependent Claim 14, now canceled and whose limitations, along with the limitations of Claim 13 (also now canceled), have been incorporated into Claim 8.

The Office Action at page 11, beginning with the fourth (4^{th}) full paragraph states:

"Regarding claim 13, Eads et al. teach wherein at least three pairs of primers are used in the polymerase reaction, one of which primer pairs is a reference primer pair that amplifies a non-methylated sequence that acts as a reference sequence (see, p. 11 for the section *Methylight* primer and probe sequences for at least 4 primer pairs including a reference primer pair).

Regarding claim 14, Eads et al. teach where the reference primer does not contain a CpG dinucleotide and does not contain a TpG dinucleotide (see p. ii for the section *Methylight* primer and probe sequences and the reference primer set for *MYOD1* where neither primer contains G and hence neither contains CpG or TpG dinucleotides.)"

Applicant respectfully disagrees with the reading of Eads et al. as applied to the further limitation previously recited in Claim 14 and now recited in Claim 8. The subject

limitation requires that the one primer pair that amplifies the reference sequence has neither a CpG dinucleotide nor a TpG dinucleotide. It is respectfully submitted that the disclosure of Eads et al. has been misred and hence, misapplied. At page ii of Eads et al., under the section heading "MethyLight primer and probe sequences" PCR primers and probes were designed for the MYOD1 and ACTB genes as the internal references. At lines 11 - 14 under that section heading it is stated

"The primer and probe sequences are listed below. In all cases, the first primer listed is the forward PCR primer, the second is the TaqMan® probe and the third is the reverse PCR primer." [emphasis added.]

The primer and probe sequences for the reference set for the MYOD1 gene appear at lines 21-24 of that section, in the order previously stated in the preceding text at lines 11-14. Specifically,

***MYOD1* forward PCR primer**: CCAACTCCAAATCCCCTCTCTAT

***MYOD1* TaqMan® probe**:

6FAM5` TCCCTTCCTATTCCTAAATCCAACCTAAATACCTCC-3`TAMRA

***MYOD1* reverse PCR primer**: **TG**ATTAATTTAGAT**TG**GGTTTAGAGAAGGA

[emphasis added.] Clearly, the reverse primer of the primer pair for the reference *MYOD1* gene contains TpG dinucleotide, in fact, two of them. Even the forward PCR primer of the primer pair for the ACTB reference gene contains TG dinucleotide (see lines 24-25 of the MethyLight section on page ii.) Accordingly, Eads et al. fails to disclose all of the limitations of Claim 8, and those claims dependent thereon, and therefore the rejection under §102(b) should be withdrawn.

Claims 1-6 have been rejected under 35 U.S.C. §102(e) as being anticipated by Olek et al (US Patent No. 6,214,556, issued April 10, 2001, and filed on September 22, 1999.) (Office Action, item 16.)

Without commenting on the propriety of the rejection, and in order to advance the prosecution of the subject application, the rejection of Claims 1-6 is rendered moot by their cancellation. Withdrawal of the rejection is respectfully requested.

Claims 1-6 have been rejected under 35 U.S.C. §102(e) as being anticipated by Olek et al (WO 2002/002809, which was filed on July 2, 2001, in English and designating the US.) (Office Action, item 17.)

Without commenting on the propriety of the rejection, and in order to advance the prosecution of the subject application, the rejection of Claims 1-6 is rendered moot by the cancellation of these claims. Withdrawal of the rejection is respectfully requested.

The Rejection of Claims 11, 18, and 23 Under 35 U.S.C. §103(a) as Being Unpatentable Over Eads et al(2000) in View of Olek et al (US 6,214,556) or Eads et al (2000) in view of Olek et al (WO 2002/002,809)

Claims 11, 18, and 23 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Eads et al(2000) *as applied to claims 1, 10, 18, and 20 above*, and further in view of Olek et al (US Patent No. 6,214,556) (Office Action, item 19.)

Claims 11, 18, and 23 have also been rejected under 35 U.S.C. §103(a) as being unpatentable over Eads et al(2000) *as applied to claims 1, 10, 18, and 20 above*, and further in view of Olek et al (WO 2002/002,809) (Office Action, item 20.)

The rejections are respectfully traversed and will be addressed simultaneously.

Initially, the two obviousness rejections as they apply to dependent Claim 23 are rendered moot by that claim's cancellation. Hence the following remarks are directed to dependent Claims 11 and 18.

Secondly, it is not clear from the statement of the rejection regarding reliance on Eads et al. "*as applied to claims 1, 10, 18, and 20 above*" what is exactly meant. Does the Examiner mean that part of the Eads et al. disclosure that was relied upon in the §102 rejections?, as there is no prior §103(a) rejection of claims 1, 10, 18, and 20 over Eads et al. The statement of the 103 rejections is unclear.

Notwithstanding, in view of the fact that Claims 11 and 18 ultimately incorporate all of the limitations of base independent Claim 8, now amended, and Claim 8 has not been rejected under §103(a), the rejection of Claims 11 and 18 should be withdrawn.

Applicant adds the following remarks. By virtue of the fact that dependent Claims 11 and 18 incorporate all of the limitations of Claim 8, amended, then the same reasons detailed above regarding the deficiency in the primary reference Eads et al. in the traversal of the §102(b) rejection of Claim 8 and those claims dependent thereon, are applicable here and are incorporated in their entirety. Namely, Eads et al. fails to disclose in a method for CpG methylation analysis amplifying one or more nucleic acids of the treated nucleic acid in a polymerase enzyme reaction by means of at least three primer oligonucleotide pairs, *wherein one primer pair does not contain a CpG dinucleotide and does not contain a TpG dinucleotide and amplifies a reference sequence* and the other primer pairs are methylation specific primers.... Moreover, Eads et al. provides no suggestion or appreciation for the design of a primer pair for amplifying a reference

sequence, wherein that primer pair contains no CpG dinucleotides and no TpG dinucleotides. Accordingly, absent ancillary art, Eads et al. is not seen to render obvious the claimed subject matter of Claims 11 and 18, as amended.

The two Olek et al. publications do not cure the deficiencies in the teachings of Eads et al. Both Olek et al. disclosures were relied upon solely for aspects pertaining to detection methods for PCR amplificates. Absent ancillary art, these rejections cannot be maintained. Therefore, in view of the present claim amendments and remarks, withdrawal of the §103(a) rejections is believed to be proper.

Claims 1-24 Rejected Provisionally for Obviousness-Type Double Patenting Over Claims 1-35 of Copending Application No. 10/493,727

Claims 1-24 have been rejected provisionally on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-35 of copending Application No. 10/493,727. (Office Action, item 22.) The Office Action states that while "the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the copending '727 application are specie methods which use primers to ATC for analysis of methylation status, which anticipate the generic methods of the instant application which use primers for analysis of methylation status."

Claims 1-7, 12-14, and 19-24 have been canceled.

Claims 8-11 and 15-18, have been amended herein in order to advance the prosecution towards allowable subject matter. In view of the present claim amendments the rejection is respectfully traversed and reconsideration is requested.

Claim 8, amended herein, recites a preferred embodiment as described, e.g., at specification page 12, beginning at line 14, and as illustrated in Figure 3 of the application.

More specifically, the embodiment of Claim 8 requires, in part, [step b] amplifying one or more nucleic acids of the treated nucleic acid in a polymerase enzyme reaction *by means of at least three primer oligonucleotide pairs, wherein one primer pair does not contain a CpG dinucleotide and does not contain a TpG dinucleotide and amplifies a reference sequence and the other primer pairs are methylation specific primers*, and further wherein the amplificates formed from each species of primer pairs differ respectively in at least one of length, sequence, and a detectable label selected from the group consisting of fluorescence labels, mass labels, and radioactive labels. Further, and now more specifically recited in Claim 8 is the step [step d] of determining the degree of methylation at each analyzed CpG position *from ratios of amplificates formed from each of said methylation specific primers relative to amplificates formed from said primer pair that amplifies said reference sequence*. A benefit resulting from the methodology of this particular preferred embodiment is an enhanced and more accurate level of quantitation of the degree of methylation at each analyzed CpG position in the nucleic acid sample being investigated under high-throughput conditions. Dependent Claims 9-11 and 15-18 incorporate all of these distinctive features recited in Claim 8 in its current form, as well as reciting additional patentable embodiments in their respective further limitations.

It is respectfully submitted that while both the subject application and the copending '727 application pertain to methylation analysis of nucleic acid samples and genomic samples, respectively, the instant claims of this application are patentably distinguishable from the specific embodiments claimed in the '727 application. Nowhere in claims 1-35 of the '727 application is a scintilla of overlap, either as a specie or as a genus, for the specific embodiment recited in Claim 8, as amended. Namely, wherein i)

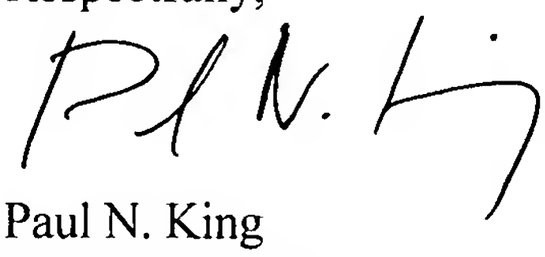
the step of amplifying one or more nucleic acids of the treated nucleic acid in a polymerase enzyme reaction is carried out by using at least three primer oligonucleotide pairs, wherein one primer pair does not contain a CpG dinucleotide and does not contain a TpG dinucleotide and amplifies a reference sequence and the other primer pairs are methylation specific primers, and ii) the step of determining the degree of methylation at each CpG island, or position, is determined from ratios of the amplificates formed from each of the MSP pairs to the amplificates formed from the primer pair not containing a CpG dinucleotide nor a TpG dinucleotide and that amplifies the reference sequence. While assuredly the methodology covered by the pending claims of the '727 application results in a patentably useful method of cytosine methylation analysis, those claimed embodiments accomplish the desired quantitative analysis in a manner that is different and distinguishable from Claim 8 herein and the claims depending therefrom. Reconsideration and withdrawal of the provisional rejection is respectfully requested.

In the alternative, if this rejection stands after being reconsidered, Applicant requests that the rejection be held in abeyance until an indication of allowable subject matter is given in the application.

Conclusion

In view of the foregoing amendments and remarks, it is believed that all objections and rejections have been addressed and overcome, and an indication of allowable subject matter is earnestly sought.

Respectfully,



Paul N. King
Reg. No. 29,259

Filed: November 7, 2007

Attachment: Information Disclosure Statement
Supplemental Declaration